

CBER Nonclinical Study Data Review Considerations

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Disclaimer

My comments are an informal communication and represent my own best judgement. These comments do not bind or obligate FDA.

Offices Conducting Nonclinical Study Review

- ***Office of Vaccines Research and Review (OVRR)***
- Office of Tissues and Advanced Therapies (OTAT)
- Office of Blood Research and Review (OBRR)

OVR: Products Reviewed

- Vaccines for prevention or treatment of infectious disease
- Allergenic immunotherapies
- Live biotherapeutic products:
 - E.g. Fecal microbiota for transplantation
- Bacteriophage products



OVR: *In Vivo* Nonclinical Studies

- Single and repeat-dose toxicology
- Developmental and reproductive toxicology (DART)
- Genotoxicity, safety pharmacology (allergenics)
- Immunogenicity
- Proof-of-concept, effectiveness, Animal Rule
- Biodistribution
- No chronic toxicity or carcinogenicity

OVRR: Data Considerations

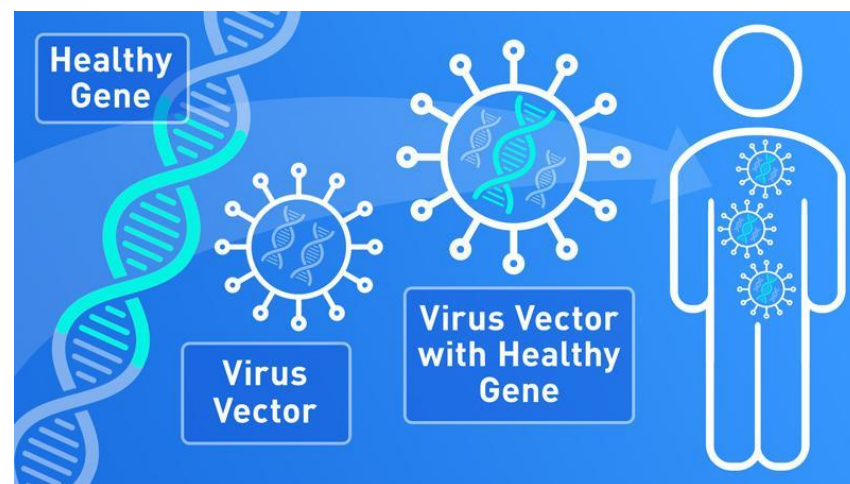
- Timing of endpoints following vaccinations
- Draize Scoring
- Body temperature
- Acute phase reactants
- Immunogenicity/Serology Assays
- Injection site histology

Offices Conducting Animal Review

- Office of Vaccines Research and Review (OVRR)
- ***Office of Tissues and Advanced Therapies (OTAT)***
- Office of Blood Research and Review (OBRR)

OTAT: Products Reviewed

- Stem cell and stem-cell-derived products
- Somatic cell products
- Xenotransplantation products
- Certain devices and combination products
- Therapeutic vaccines for non-infectious indications
- Recombinant or plasma derived proteins
- Wound healing products
- Gene therapy



OTAT: Animal Studies Reviewed

- Proof-of-concept/safety/toxicity
- Cell-fate/biodistribution, typically no PK studies
- Differentiation/integration capacity
- Tumorigenicity: required for stem cell therapy
- Biocompatibility (implantable scaffolds)
- Immunogenicity (therapeutic vaccines)

OTAT: Data Considerations

- Animal model of disease/injury
- Hybrid safety and activity studies
- Distribution/biodistribution assessments
- Biocompatibility of devices

Offices Conducting Animal Review

- Office of Vaccines Research and Review (OVRR)
- Office of Tissues and Advanced Therapies (OTAT)
- ***Office of Blood Research and Review (OBRR)***

OBRR: Products Reviewed

- Modified blood components
- Hemoglobin-based oxygen carriers
- Container-closure systems
- Process-related impurities
- Excipients
- Pathogen reduction systems

OBRR: Nonclinical studies

- Focuses on biocompatibility
- Extractables and leachables testing
 - Container closure systems
- Occasionally see developmental or embryo-fetal toxicology for replacement proteins
- Proof-of-concept
- Carcinogenicity

OBRR: Data Considerations

- GLP-compliant toxicology studies only requested on a case-by-case
- Most nonclinical studies are not amenable to SEND data
- Systemic toxicity (biocompatibility, hemoglobin-based oxygen carriers),
 - Mutagenicity (impurities, extractables, leachables)

DEVELOPING SEND FOR CBER

- Collaborative workstream initiative
 - Currently SEND is not required for CBER submissions
 - Joint working team among CDISC, CBER non-clinical reviewers and industry experts has been formed to evaluate specific needs for supporting CBER submissions
 - Bi-weekly teleconferences since June 2018 and face-to-face meetings twice annually
 - Identify the gaps and discuss the needs for new domains, variables and CT code list, make recommendations to CDISC
 - Perform proof-of-concept pilot program

SEND for CBER Project Plan

Task	Start	Finish	DUR	3Q18					4Q18				1Q19			2Q19		3Q19				4Q19		
				J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D			
SEND Orientation	Jun2018	Jul2018	2 M																					
SEND Domain reviews	Aug2018	Mar2019	7 M																					
Gap Analysis	Oct2018	May2019	9 M																					
Proof of Concept Pilot	Jun2019	Sep2019	4M																					
Build Recommendation	Jul2019	Oct2019	2 M																					

